Unraveling Disease Heterogeneity: Generative Adversarial Network based Normative Modeling

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1 Introduction

Neuroimaging studies have documented structural and functional heterogeneity in the brains of patients with Alzheimer's disease (AD), traumatic brain injury, and other neurological disorders.[1,2] This heterogeneity leads to diagnostic and prognostic uncertainty, further confounding clinical treatment planning. Normative modelling, where individual-level deviations in brain measures from a reference sample are computed to infer personalized effects of disease, allows parsing of disease heterogeneity.[3] Traditional univariate normative modelling techniques like Gaussian process regression (GPR) ignore multivariate interactions between brain measures. On the other hand, multivariate deep-learning based techniques such as adversarial autoencoders (AAE) might have low specificity to disease effects as they are trained solely on the reference sample.[4] In both cases, the computed deviations might incorporate disease irrelevant effects due to inter-individual brain differences. To overcome this, we propose a GAN-based normative modeling technique that learns to synthesize individualized controls by removing disease-related variations from patient's brain measures. Deviation of the patient from the synthesized disease-free control acts as an image-based biomarker that is sensitive to disease effects and severity. The proposed method is illustrated in Fig.1.a. When applied to participants with co-morbid conditions, Fig.1.b shows that there is statistically significant difference in GAN-derived deviations in regional volumes of subjects with TBI, Hypertention, or Diabetes compared to reference participants without comorbidities. This shows the models ability to detect subtle variations in biomarker profiles and its utility in precision medicine.

References

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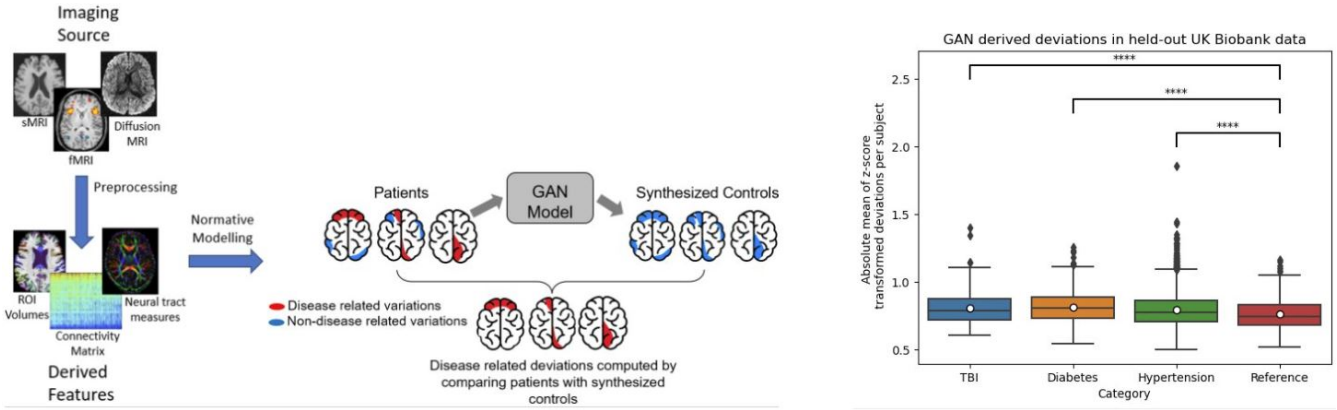

(a) (b)

Fig. 1: Proposed GAN-based normative modelling framework and associated results. a) Overview of the framework, b) Absolute mean of Z-score transformed deviations (MAZ) derived using the GAN model in healthy control reference subjects and subjects with hypertension, diabetes, and TBI, respectively. A permutation test was used to assess difference in group means.

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